Topics in Computational Inference

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9 Compartmental Models

This chapter introduces compartmental models that are widely used in pharmacokinetics. Compartmental models are defined by differential equations. They serve as a good introduction to a broader class of models called dynamical systems. This chapter contains a general introduction followed by a detailed analysis of a one compartment model.

Section 9.1 — The Compartmental Model

This section provides a brief introduction to compartmental models. Amoung the terms introduced are kinetics, rate constants, infusion, infusion rates, bolus injections, kinetic diagrams, and differential equations.

A Compartmental System

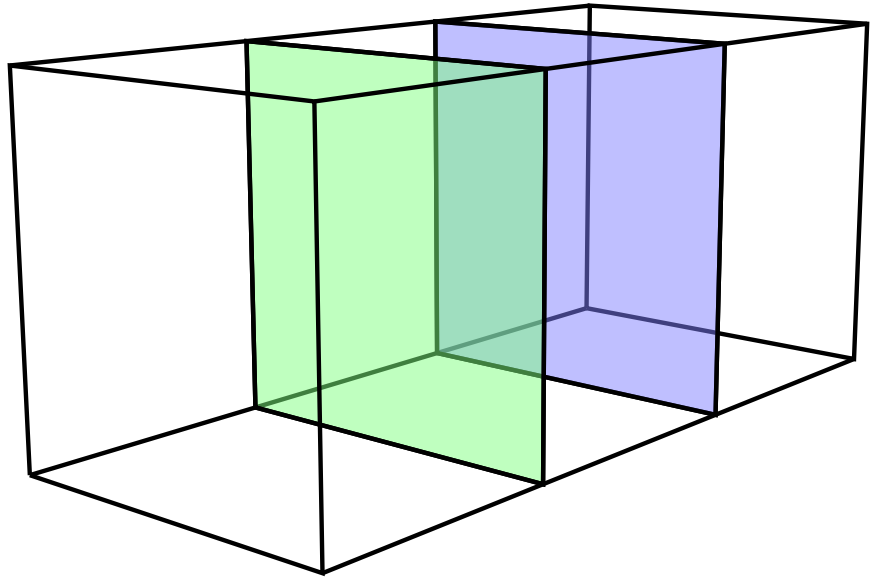


Figure 9.1: A fish tank separated into three compartments by permeable membranes.

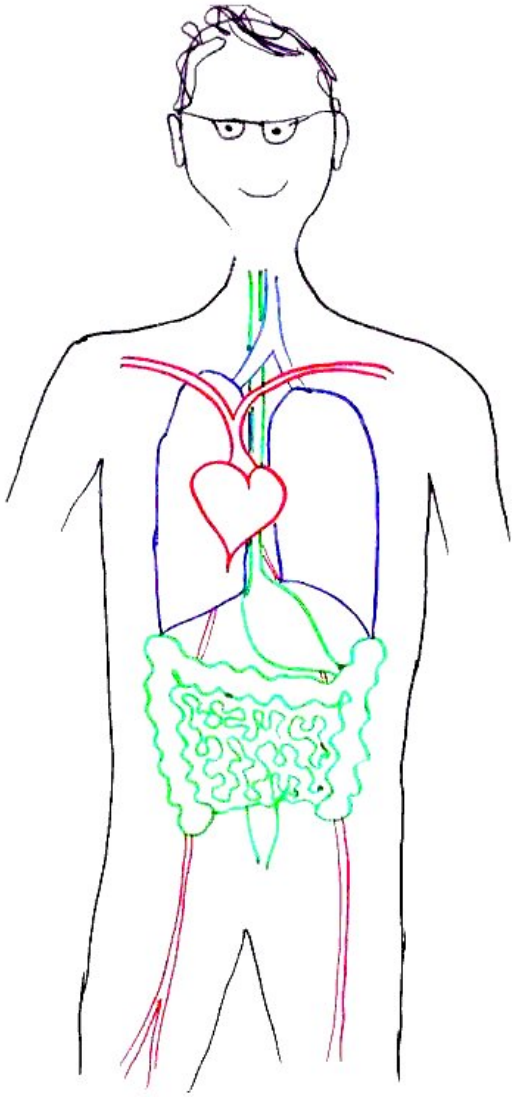
A Compartmental Model

The tank in Figure 9.1 is filled with a medium, and a substance is placed in one of the compartments in addition to the medium. This system, along with rules on the movement of the substance, is an idealized representation of a *compartmental model*. The interest is in the movement of the substance from compartment to compartment.

A More Complicated System

The fish tank model is a vast oversimplification of the system at the right. Amazingly, compartmental models often provide a good representation of the movement of a drug through the body.

The figure was drawn by daughter Diane in about the eighth grade.



Kinetics

Kinetics is a science that deals with the effects of forces upon the motions of material bodies or with changes in physical or chemical systems. Kinetics provide the rules for the movement of the substance from compartment to compartment. Here it is assumed that the movement is characterized by differential equations.

First Order Kinetics

$x(t)$ is the amount of a substance in a compartment at time t and $\dot{x}(t)$ is its derivative with respect to t. A situation where

$$\dot{x}(t) = -\theta x(t)$$

is *first order kinetics*. The parameter θ is *rate constant*.

Zero Order Kinetics

A situation where

$$\dot{x}(t) = \alpha$$

is *zero order kinetics*. The parameter α is an *infusion rate*. Imagine slowly pouring a substance into a compartment of the fish tank at a constant rate.

The Kinetic Diagram

When modeling the movement of a drug in the human body, the first step is to create a *kinetic diagram* as follows:

1. Determine what components of the system are to be represented by a compartment.

2. Determine the inputs to the system and the associated rate constants. Inputs may be zero order or bolus injections.

3. Determine the possible transfers between compartments and the rate constant associated with each transfer. Transfers between compartments are first order.

A Model with Zero and First Order Kinetics

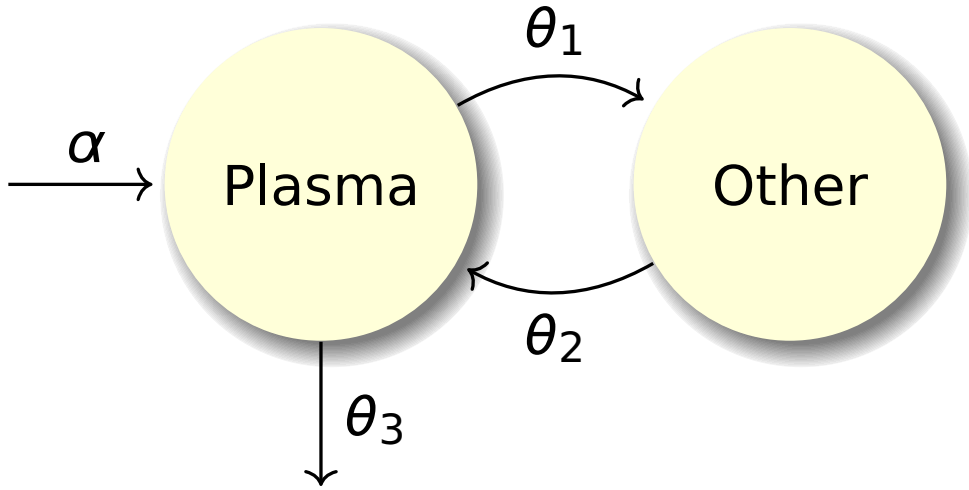


Figure 9.2: A model with both zero and first order kinetics

My convention is that an arrow originating from a compartment is a first order transfer, and other arrows represent zero order inputs.

Implied Differential Equations

Let $x_1(t)$ and $x_2(t)$ represent the respective amounts of substance in the two compartments at time t. The differential equations implied by the diagram of Figure 9.2 are

$$\begin{bmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \end{bmatrix} = \begin{bmatrix} \alpha \\ 0 \end{bmatrix} + \begin{bmatrix} -\theta_1 - \theta_3 & \theta_2 \\ \theta_1 & -\theta_2 \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \end{bmatrix} \tag{9.1.1}$$

Things to be Learned

Things that might be learned, depending on the situation, are

- the uptake rate and steady state level of a heavy metal in animal tissue;
- the average time a drug stays at its site of action;
- the relative bioavailability of two drugs;
- the relationship between drug concentration in a compartment and symptom relief.

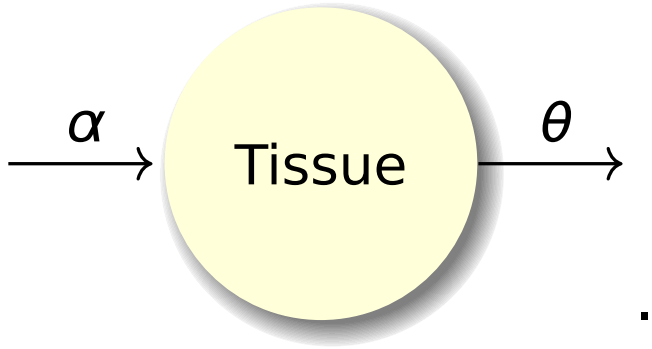
Regardless of the situation, one must estimate the parameters and check that the model is at least plausible.

Section 9.2 — Modeling Mercury Pollution in Fish

This exercise is to model the mercury content in the tissue of a fish that is swimming in water polluted with mercury. A compartmental model is used to describe the absorption and elimination of mercury by the tissue of the fish over time. The model is fit to the data to find estimates of the parameters and a formula for the concentration of mercury in the fish.

The Kinetic Diagram

The kinetic diagram is



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The arrow coming from the left represents a zero order input. Since the body of water is essentially infinite relative to the mass of the fish, zero order input seems plausible. The parameter α is an infusion rate and θ is an elimination rate constant.

The Differential Equation

Time t is measured in days. At time $t = 0$ the fish is moved from uncontaminated water into polluted water. $x(t)$ represents the concentration of mercury in the tissue of the fish at time t. The differential equation is

$$\dot{x}(t) \quad = \quad \alpha - \theta\, x(t)$$

where $x(0) = 0$.

The Solution

Steps to the solution are

$$\begin{aligned}
\dot{x}(t) + \theta\, x(t) &= \alpha \\
(\dot{x}(t) + \theta\, x(t)) \exp(\theta\, t) &= \alpha \exp(\theta\, t) \\
x(t) \exp(\theta\, t) &= (\alpha/\theta) \exp(\theta\, t) + d \\
x(t) &= (\alpha/\theta) + d \exp(-\theta\, t) \\
x(t) &= (\alpha/\theta)(1 - \exp(-\theta t))
\end{aligned}$$

That $x(0) = 0.0$ implies that the constant of integration d is $-\alpha/\theta$.

A Reparameterization

It is common to reparameterize a solution to improve interpretation and simplify computation. For the present example, a parameterization might be

$$\theta_1 = \alpha/\theta$$
$$\theta_2 = \theta$$

The response formula becomes

$$x(t) = \theta_1(1 - \exp(-\theta_2 t)). \qquad (9.2.1)$$

Now θ_1 represents the steady state concentration or the concentration where the intake equals the elimination. Replacing the ratio also simplifies model fitting. Any one-to-one reparameterization would be legal.

The data

The data are unpublished from the Savannah River Laboratories:

i	Day t_i	Concentration Y_i
1	0	0.0000
2	1	0.1352
3	2	0.2168
4	3	0.2545
5	4	0.3258
6	6	0.3313

The Observational Model

The observational model is

$$Y_i = x(t_i) + \epsilon_i$$

where $x(t)$ is from Equation (9.2.1). Under the assumption that the ϵ_i are uncorrelated with equal variances, it is appropriate to use least squares to estimate the parameters.

Fitting the model to data

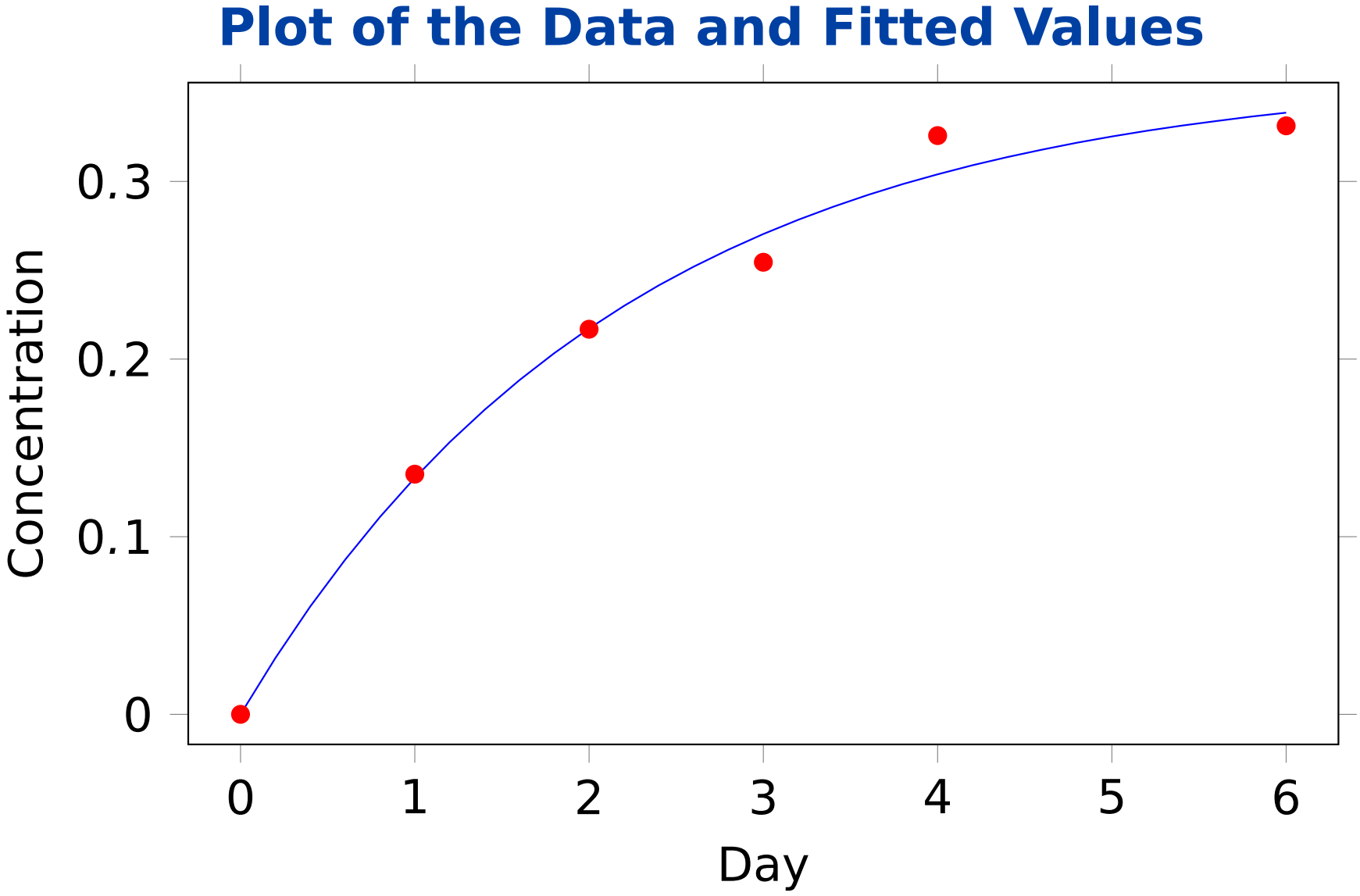
To fit the model to the data we find the values of θ_1 and θ_2 that minimize

$$\sum_{i=1}^{6}(Y_i - x(t_i))^2.$$

The minimizing values are the *least squares estimators* of θ_1 and θ_2.

The Gauss-Newton Algorithm

The model is typically fit to data using an optimization algorithm such as differential evolution or the Gauss-Newton algorithm.


Plot of the Data and Fitted Values
Concentration
0
0.1
0.2
0.3
0
1
2
3
4
5
6
Day

An Exercise

Exercise 9.1. The barley data are

Nitrogen(10kg/ha)	*Yield(kg/ha)*			
0	23	22	19	21
3	31	35	31	34
6	37	40	38	38
9	40	42	40	40

This is not a compartmental model, but the methodology is the same. Let t be the amount of applied nitrogen and $x(t)$ the related expected yield of barley. Let

- a = expected yield with no applied nitrogen
- b = upper bound on yield
- r = rate of response

Assume the differential equation

$$\dot{x}(t) = r(b - x(t))$$

where $x(0) = a$. Your exercise is to

1. solve the differential equation
2. (optional) reparameterize
3. fit the model to the data using your modification of the *C++* code provided

Hand in your solution of the differential equation, program listing, and program output.